RESPONSE

I. Status of the Claims

Prior to the fourth Action, claims 1-14, 20-30 and 34-48 were pending. Presently, claims 39-42 have been amended without prejudice or disclaimer to even further improve their clarity. No claims have been canceled. Claim 49 has been added, which is fully supported by the application as filed and unified with the pending claims.

Claims 1-14, 20-30 and 34-49 are therefore in the case. According to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

II. Support for the Claims

Support for the amended and new claim exists throughout the original application as filed. In light of the claims canceled to date, no fees should be due for entry of the new claim, however, any small entity fees deemed necessary should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4001.002282.

Each of claims 39-42 has been revised to even further clarify that the at least a first anti-aminophospholipid antibody of the claimed kits is "at least a first anti-cancer agent". This is supported throughout the specification, *e.g.*, at least at page 32, lines 7-8. The anti-cancer agent in claims 39-42 has also been defined as at least a second anti-cancer agent "other than" the anti-aminophospholipid antibody that forms the first anti-cancer agent. This is also supported by the foregoing text in the specification at page 32, with additional support in Section G, where the specification states "each of the anti-aminophospholipid antibody and other anti-cancer agent components of the kit" (specification at page 104, lines 22-24, emphasis added).

New claim 49 is directed to a kit comprising a first anti-cancer agent in the form of an antibody, or an antigen-binding fragment thereof, which binds to phosphatidylethanolamine, in

combination with a second, distinct anti-cancer agent, *i.e.*, a second anti-cancer agent other than the first antibody, or an antigen-binding fragment thereof, which binds to phosphatidylethanolamine. Claim 49 is thus based upon claim 1 and extensive sections of the specification as filed.

It will therefore be understood that no new matter is included in the amended claims or the new claim.

III. Restriction and Species Issues

The Action states that claims 2, 13, 30 and 36-38 "are withdrawn from further consideration, as being drawn to nonelected species. Applicant timely traversed the restriction (election) requirement in Paper No. 14" (Fourth Action at page 2). The Action's statements are in error.

First, the original species elections were made without traverse. Second, claims drawn to initially non-elected species cannot be withdrawn from "further" consideration, but are to be rejoined upon the allowance of one or more generic, sub-generic or linking claims.

IV. Rejection 1, 3-12, 14, 20-29, 34, 35 and 39-42 Under 35 U.S.C. § 112 First Paragraph

The fourth Action newly rejects claims 1, 3-12, 14, 20-29, 34, 35 and 39-42 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Although Applicants respectfully traverse, the rejection is overcome.

Applicants note that examined claims 43-48 are free from this ground of rejection and have thus been accepted as fully complying with the written description requirement. Rejected claims 1, 3-12, 14, 20-29, 34, 35 and 39-42 also comply with the written description requirement for at least the same reasons as the Office finds claims 43-48 to be acceptable. In the unlikely event that the Office considers a written description rejection of claims 43-48, this would have to

be made as part of a non-final Official Action, being a new ground of rejection not necessitated by Applicants' amendment or untimely submission of references.

Despite the finding in all three earlier Official Actions that all claims comply with the written description requirement, the present indication that claims 43-48 comply with the written description requirement, the significant details in the specification, the knowledge and level of skill in the art, including a number of issued U.S. patents in the relevant fields, and the assessment of the Action itself at pages 10 and 11, the fourth Action takes the position that claims 1, 3-12, 14, 20-29, 34, 35 and 39-42 lack adequate written description support. In particular, the fourth Action alleges that the disclosure lacks sufficient written description support for compositions and kits comprising any or all types of antibodies that bind to any aminophospholipid even further comprise such targeting antibodies that binds to surface expressed or localized components such as ICAM-1, PAMA[1], TIE, pleiotropin, *etc.*, as recited in claims 22-25 (fourth Action at page 3).

Not only does this rejection ignore the details in the specification, but it is significantly in conflict with issued U.S. patents, controlling case law and the written description guidelines. For example, the rejection improperly confuses the overall written description with the working examples, ignores issued U.S. patents with same specification and priority date as the present case, ignores issued U.S. patents incorporated by reference into the specification and contradicts its own assessment of the art as set forth at pages 10 and 11. The rejection is thus *prima facie* improper and should be withdrawn.

In regard to "any or all types of antibodies that bind to any aminophospholipid", questioned in the Action at page 3, the Action itself establishes that antibodies that bind to

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[1]PAMA is not recited in any pending claim.

aminophospholipids were known in the art prior the present invention. In particular, the fourth Action at pages 10 and 11 refers to "the conventional practice of preparing monoclonal antibodies directed to phosphatidylserine" and "the expectation of success when preparing monoclonal antibodies directed to aminophospholipids".

As to "the combined features of the claimed kits", questioned in the Action at page 4, the Action itself again shows that combination therapy was known in the art prior the present invention. Notably, the fourth Action at page 11 refers to "more evidence on the record to substantiate the expectation of success when preparing monoclonal antibodies directed to aminophospholipids and further using the combination therapy of two cytotoxic agents to improve the optimum clinical effect". Therefore, the rejection is *prima facie* improper.

The present application has the same specification, was filed on the same day and claims priority to the same provisional applications as U.S. Application Serial No. 09/351,543, which issued as U.S. Patent No. 6,406,693 ("the '693 patent"; Attorney Docket No. 4001.002200). The '693 patent issued with claims directed to methods of killing tumor vascular endothelial cells, inducing coagulation in tumor vasculature, and treating animals and humans having vascularized tumors using any or all types of antibodies that bind to any aminophospholipid (claims 1-27, 41-46, 49-60, 62 and 63).

The issued claims in the '693 patent also include methods of treating animals and humans having vascularized tumors by administering any or all types of antibodies that bind to any aminophospholipid and further simultaneously or sequentially administering a therapeutically effective amount of at least a second anti-cancer agent (claims 28-41, 47, 48 and 61), including an antibody-therapeutic agent construct in which the targeting antibody binds to a surface-expressed component of intratumoral vasculature such as ICAM-1, PSMA, a TIE and pleiotropin

(claim 34). Thus, the claims issued in the '693 patent represent the *in vivo* treatment methods resulting from administration of the components of the presently claimed kits.

Issuance of the '693 patent, including the same claim language as currently rejected, and yet earlier determined to be patentable, compels a finding of patentability for all rejected claims. 35 U.S.C. § 282; *Biovail Corp. International vs. Andrx Pharmaceuticals Inc.*, 57 USPQ2d 1813 (Fed. Cir. 2001). Applicants are aware that each application is examined on its own merits. However, as the specifications are the same, the priority dates are the same, and the claim language at issue is the same, the merits are the same.

Applicants have also been informed by the present Examiner[2] that issuance of *in vivo* treatment method claims does not indicate that the compositions used in the treatment methods have written description support in the same specification. This is nonsensical. The written description requirement mandates that the claimed subject matter be described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention (fourth Action at page 3). To be in possession of claims drawn to cancer treatment by simultaneously or sequentially administering an antibody to an aminophospholipid and at least a second anti-cancer agent, one must be in possession of the antibody and the anti-cancer agents themselves.

As the Office has already determined the method claims of the '693 patent to be patentable, and thus supported by an adequate written description, the presently rejected kit claims must also be supported by an adequate written description. As issued U.S. patents have a presumption of validity under 35 U.S.C. § 282, grant of the '693 patent compels withdrawal of the present rejection:

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[2]In a teleconference held April 21, 2004 for related Application Serial No. 09/351,149.

> "When multiple patents derive from the same initial application, the prosecution history regarding claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain same claim limitation".
>
> *Biovail Corp. International vs. Andrx Pharmaceuticals Inc.*, 57 USPQ2d 1813, 1816 (Fed. Cir. 2001).

In addition, although the first anti-cancer agents are conjugates rather than antibodies, Applicants further refer to the issued composition and method claims in U.S. Patent Nos. 6,312,694 ("the '694 patent"; Attorney Docket No. 3999.002300), 6,783,760 ("the '760 patent"; Attorney Docket No. 3999.002399) and 6,818,213 ("the '213 patent"; Attorney Docket No. 3999.002382), which all further support the patentability of the present claims.

As to the second anti-cancer agents in particular, Applicants also point out that anti-cancer agents in the form of antibody-therapeutic agent constructs comprising a targeting antibody, or antigen-binding fragment thereof, that binds to a surface-expressed, surface-accessible or surface-localized component of a tumor cell, tumor stroma or tumor vasculature, operatively linked to a therapeutic agent, are themselves patented and that such patents were specifically incorporated into the present specification by reference when the application was filed. For example, see U.S. Patents Nos. 5,855,866; 5,776,427; 5,863,538; 5,660,827; 6,004,554; 5,877,289; 5,965,132; 6,093,399; 6,004,555 and 6,036,955 (see **Section A** and **Section J4** of the specification, in particular).

Moreover, given that entry and maintenance of the present rejection is tantamount to questioning the validity of the '693, '694, '760 and '213 patents, in addition to the validity of the patents incorporated into the specification by reference, Applicants respectfully request that any further rejections be signed by the Group Director. MPEP 1701; 2242 (see MPEP 2242 at page 2200-43, column 2).

The written description rejection under § 112, first paragraph is thus overcome and should be withdrawn.

V. Withdrawal of Rejection Under 35 U.S.C. § 102(e)

Claims 1, 3-12, 14, 20-22 and 39-43 in the present application are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,300,308 to Schroit ("Schroit"). Although Applicants respond in full below, the Office has already re-assessed Schroit in a co-pending application and withdrawn the § 102(e) rejection based on the same reasoning set forth in this Action. Accordingly, the present rejection is improper and should also be withdrawn.

In co-pending application Serial No. 09/351,149 ("the '149 application"), the Office mailed a Fourth and Non-Final Official Action ("the Fourth Action") on October 22, 2002. The Fourth Action in the '149 application also included a § 102(e) rejection over Schroit, the reasoning of which was the same as that set forth in the present application (compare the respective sections of the Actions, where the text is almost exactly the same).

Applicants submitted a response in both applications on April 22, 2003, addressing the § 102(e) rejections in substantially the same manner. In the '149 application, the § 102(e) rejection over Schroit was withdrawn (fifth Action mailed July 15, 2003 in the '149 application, see fifth Action throughout, bottom of page 2, and page 3, third paragraph).

The reasoning of the Office concerning Schroit of record in the present application, which dates back to October 22, 2002, is thus inconsistent with the reasoning of the Office in the '149 application, in which the § 102(e) rejection over Schroit was withdrawn. Accordingly, the present rejection is unfounded and should also be withdrawn.

VI. Rejection of Claims 1, 3-12, 14, 20-22 and 39-43 Under 35 U.S.C. § 102(e)

Claims 1, 3-12, 14, 20-22 and 39-43 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Schroit. Although Applicants respectfully traverse, the Action's concerns are overcome.

A. The Office has Re-assessed Schroit and Withdrawn the § 102(e) Rejection

As set forth above, the Office has reconsidered Schroit in the '149 application and withdrawn the § 102(e) rejection based on the same reasoning as advanced in the present case. In particular, the Office described Schroit as failing to disclose "suitable antiphospholipid antibodies in combination with a second anticancer agent" ('149 application, fifth Action at page 3).

Applicants earlier pointed out the significant inconsistency between the interpretation of Schroit in the '149 application and the interpretation of Schroit in the present application, but the Office has yet to explain the ongoing differences. Accordingly, should the present rejection be maintained, Applicants respectfully request that the Office explain why Schroit was held not to teach a kit with two anti-cancer agents in the '149 application, but is still held to contain such a teaching in the present application.

In addition, in the present application, the fourth Action later states, "Schroit fails to use an unconjugated antibody in combination with a second anticancer agent and/or explicitly use a second anticancer agent different than the first dose of his first anticancer agent" (fourth Action at page 9). This statement in the fourth Action itself also contradicts the § 102(e) rejection that has been maintained.

B. Response on the Merits

The following response should not be interpreted as an acquiescence that a proper *prima facie* rejection was established, nor that the effective filing of date Schroit is earlier than the effective filing date of the present application, nor as waiving any rights to establish a date of invention earlier than the effective filing date of Schroit.

The fourth Action at page 6 states that claims 39-43 do not recite a second anti-cancer agent "other than" the first anti-cancer agent. This is *prima facie* incorrect for claim 43, which depends on claim 1 and thus contains the "other than" recitation. The scope of claims 39-42 as covering an antibody that binds to an aminophospholipid and a second anti-cancer agent "other than" the anti-aminophospholipid is believed to be clear from the specification, optionally in light of the prosecution history. Nonetheless, Applicants appreciate the Examiner's attention to detail and claims 39-42 have been revised to expressly recite that the second agent is an anti-cancer agent "other than" the anti-aminophospholipid antibody.

The Action's discussion of claims 39-42, as set forth above, serves to highlight the Action's error regarding the other rejected claims, which clearly recite a first anti-cancer agent in the form of an antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid and a second anti-cancer agent "other than" the first antibody or an antigen-binding fragment thereof. Despite the clear recitation of a second anti-cancer agent "**other than**" the first antibody, the fourth Action continues the position that "the scope of a second anticancer agent 'other than' at least a first antibody, encompasses a simple second dose of the first anti-cancer agent" and that "the second cancer agent can be the same as the first cancer agent" (fourth Action at page 7). Not only is this incompatible with plain English, it is exactly the position that has already been withdrawn in the '149 application.

Applicants have repeatedly stressed that the claim language a second anti-cancer agent "other than" the first antibody **cannot** be held to mean "a simple second dose of the first anti-cancer agent". Not only is "other than" not a synonym for "the same", it is the opposite of "the same". Webster's collegiate dictionary defines "other" and "other than" as follows:

> **Other**, being the one remaining or not included; being the one or ones distinct from that or those first mentioned or implied; in the every day sense, as "not the same: DIFFERENT" or "ADDITIONAL"; "one that remains of two or more"; "a thing opposite to or excluded by something else"; "a different or additional one"
>
> **Other than**, "with the exception of: EXCEPT FOR, BESIDES"
>
> Merriam-Webster's Collegiate Dictionary, Tenth Edition (capitals as in original).

Therefore, the claim term means the first anti-cancer antibody and a second anti-cancer agent "other than, distinct from, not the same as, different to, in addition to, opposite to, excluding, with the exception of, except for or besides" the first anti-cancer antibody.

The Action's comments on the specification at pages 19, 32 and 35 have already been shown to be misplaced (fourth Action at page 7), particularly as this issue was first raised in the context of a clarity rejection under 35 U.S.C. § 112, second paragraph, which has been withdrawn. The entire specification, including the text at page 32, makes it clear that the choice of the terms "first" or "second" in regard to the antibodies and anti-cancer agents is simply a matter of semantics, and in no way indicates that the first and second, distinct anti-cancer agents are in fact the same. By analogy, the terms "a first fruit and a second, distinct fruit" and "a first fruit and a second fruit other than said first fruit" can mean an apple and an orange, but cannot mean two apples. The specification at page 32 simply explains that it does not matter to which example the terms "first and second" are applied. Thus, in the same analogy, one can refer either to a first apple and a second orange, or to a first orange and a second apple, as both phrases mean

a first fruit and a second, distinct fruit. Such phrasing permits neither two apples nor two oranges.

In light of the plain meaning of "other than", supported by the dictionary definition set forth above, which is consistent with the ordinary use of this term in the specification, should the present rejection be maintained, Applicants respectfully request that the Office cite an authority on the English language that supports the position that "other than" means "the same as". Applicants further respectfully request that the Office explain why Schroit was held not to teach a kit with two distinct anti-cancer agents in the '149 application (see fifth Action at page 3).

Aside from the improper claim interpretation, which underlies most of the rejection, the Action's additional comments also fail to support the § 102 rejection. Applicants incorporate by reference the detailed in their earlier responses reasoning regarding these issues. In regard to the particular errors in the fourth Action, Applicants respond as follows.

The Action first states, "each antibody composition of Schroit contains an antibody directed to PS and a polypeptide such as BCG or diphtheria toxoid" (fourth Action at page 5). This is not correct. The antibody compositions of Schroit contain an antibody. The polypeptides such as BCG or diphtheria toxoid are conjugated to PS, the antigen, and administered to produce the antibody.

The Action next states, "Schroit teaches combination of his antibodies with a secondary anti cancer agents [*sic*] such as BCG or diphtheria toxoid (col 8, lines 65-67)" (fourth Action at page 6). This is not correct either. At column 8, lines 65-67, Schroit again concerns coupling the antigen, PS, to a carrier such as BCG or diphtheria toxoid. The PS-carrier conjugate is one composition. This can be administered to produce an anti-PS antibody. The anti-PS antibody is <u>not</u> combined with BCG or diphtheria toxoid.

At page 8, the fourth Action discusses Schroit from column 7, line 67 to column 8, line 1. As pointed out earlier, this section of Schroit concerns one container with a PS composition and another container including "a matrix, solution, or other suitable delivery device" for applying "the composition" to the body. That is, one PS composition, optionally with one delivery device. This does not constitute a kit with a first antibody and second, distinct anti-cancer agent, as in the presently claimed invention.

Finally, as to Schroit's reference to "separate moieties to be conjugated by user of the kit" at column 6, lines 50-51 (fourth Action at page 8), the same sentence shows that this concerns "antibody-label conjugates" (Schroit at column 6, line 49). In the present application, the Office will recall that kits comprising antibody-label conjugates were found to be drawn to a patentably distinct invention and are not pending.

In summary, there is no teaching or suggestion in Schroit of a kit comprising a first anti-cancer agent in the form of an anti-aminophospholipid antibody, or antigen-binding fragment thereof, and a second anti-cancer agent other than the first anti-aminophospholipid antibody or fragment.

The § 102(e) rejection over Schroit is therefore overcome and should be withdrawn.

VII. Withdrawal of Rejection Under 35 U.S.C. § 103(a)

In the third Action in the present application, claims 1, 3-12, 14, 19-29, 34, 35 and 39-43 were rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Schroit in view of U.S. Patent No. 5,632,991 to Gimbrone ("Gimbrone") and Umeda *et al.*, *J. Immunol.*, 143:2273-2279, 1989, ("Umeda").

The fourth Action withdraws the § 103(a) rejection over Schroit Gimbrone and Umeda. Thus, the claimed invention is thus acknowledged to be patentable over Schroit Gimbrone and Umeda in combination.

VIII. Rejection of Claims 1, 3-12, 14, 19-29, 34, 35 and 39-43 Under 35 U.S.C. § 103(a)

The fourth Action now rejects claims 1, 3-12, 14, [3]19-29, 34, 35 and 39-48 under 35 U.S.C. § 103(a) as allegedly being legally obvious over Schroit in view of Gimbrone, Umeda and an additional reference said to be "Bayer US Patent 4,925,922", which is actually "Byers". Although Applicants respectfully traverse, the Action's concerns are overcome.

A. The Claims are Patentable Over Schroit, Gimbrone and Umeda

The earlier § 103(a) rejection, which cited only Schroit, Gimbrone and Umeda, has been withdrawn. Thus, the Office has indicated that claims 1, 3-12, 14, 19-29, 34, 35 and 39-48 are patentable over Schroit, Gimbrone and Umeda in combination. Key questions to answer, therefore, are (1) whether the combination of Schroit, Gimbrone, Umeda and Byers is proper; and (2) whether the addition of Byers cures the admitted lack of teaching or suggestion in Schroit, Gimbrone and Umeda. Applicants address these issues below, in addition to all aspects of the rejection.

B. Byers is Improperly Combined and Does Not Strengthen the Rejection

The references have been improperly combined, including the improper combination of Schroit, Gimbrone and Umeda, and the new addition of Byers.

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[3]Claim 19 is no longer pending.

Schroit, Gimbrone and Umeda were earlier said to be combinable because the three cited references were viewed to be in the same field of endeavor and because "each reference is directed to specific receptor molecule on the surface of human vascular endothelial cells associated with vascularized tumor" (third Action at page 5). Applicants traversed the combination for reasons including that the references had been improperly characterized; the alleged motivation to combine was derived only from the present application and not from the cited art; and the combination was formulated with hindsight. The rejection was withdrawn.

The Action now adds Byers to Schroit, Gimbrone and Umeda. Byers is cited as showing monoclonal antibodies conjugated to toxins alone or in combination with an unconjugated monoclonal antibody and the expectation of success in improving the clinical efficacy of such process (fourth Action at page 10). The motivation to combine is said to be that the teachings of Schroit, Gimbrone, Umeda and Byers "are in the same field of endeavor as they are all directed to the field of antibody immunology" (fourth Action at page 10).

The field of antibody immunology is vast and the mere presence of four references within the field of antibody immunology does not provide the required motivation to combine.

Schroit concerns PS and reports that, as opposed to the situation in normal cells, PS may appear at the surface of tumor cells (Schroit throughout, *e.g.*, column 16, lines 27-33). Gimbrone concerns E-selectin expression on activated endothelium in certain diseases or infections, particularly in inflammation, and in connection with the metastatic spread of tumor cells (Gimbrone throughout, *e.g.*, Abstract, column 4, line 57 to column 5, line 7). Umeda concerns the direct immunization of PS-coated *Salmonella* into mouse spleen and stereo-specific aspects of antigen recognition by monoclonal antibodies (Umeda throughout, *e.g.*, Abstract and page 2274).

Byers concerns immunotoxins that bind to a first epitope of a tumor cell surface antigen and methods to potentiate the cytotoxicity of some of those immunotoxins by co-administering an immunoglobulin that binds to a second, distinct epitope on the tumor cell surface antigen (Byers throughout, *e.g.*, Abstract, claims, paragraph bridging columns 4 and 5). The combination treatment methods of Byers are limited to methods to potentiate the cytotoxicity of immunotoxins by triggering or enhancing "endocytosis of the toxic moiety" (Byers at column 6, lines 30-42).

The Action at page 11 further takes the position that Schroit, Gimbrone, Umeda and Byers are combinable because they are "useful for the same purpose". This statement is in error and fails to support the proposed combination or the resultant § 103 rejection. The purpose of Schroit is immunization with PS-polypeptide conjugates to generate PS-specific antibodies, which may bind to tumor cells; the purpose of Gimbrone is treat diseases and infections associated with E-selection expression on activated endothelium, particularly inflammation; the purpose of Umeda is direct intrasplenic immunization with PS-coated *Salmonella* and stereo-specific analysis of PS recognition by antibodies; and the purpose of Byers is to potentiate the cytotoxicity of immunotoxins by enhancing endocytosis of the toxic moiety.

These four references are therefore not directed to the same purpose, but rather have significantly different content and purposes. The references have therefore been improperly combined and the rejection is *prima facie* improper and should be withdrawn.

Importantly, even if combined, Schroit, Gimbrone, Umeda and Byers do not teach or suggest the presently claimed invention of a kit comprising a first antibody, or an antigen-binding fragment thereof, which binds to an aminophospholipid and a second anti-cancer agent other than such a first anti-aminophospholipid antibody or fragment.

In attempting to show a suggestion towards the claimed kits in Schroit, the Action states, "Schroit encourages the use of his compositions in combination with other therapeutic modalities" (fourth Action at page 11). No indication is given as to where such encouragement is believed to exist in Schroit. Applicants have studied Schroit and cannot identify any encouragement to use the compositions in combination with other therapeutic modalities. In fact, Schroit fails to teach or suggest the kits of the claimed invention, and the lack of a § 103 rejection of any claim based upon Schroit *alone* is an admission that Schroit does *not suggest* the presently claimed invention.

The Action therefore relies on Gimbrone, Umeda and Byers to cure the deficiencies of Schroit. However, Gimbrone, Umeda and Byers have been improperly combined with Schroit, and even if properly combined, Schroit, Gimbrone, Umeda and Byers together fail to teach or suggest the kits of the present invention.

Neither Gimbrone, Umeda nor Byers teach or suggest the claimed kits or second anti-cancer agents, or in any way cure the deficiencies of Schroit. Gimbrone is silent as to antibodies that bind to aminophospholipids (fourth Action at page 10). Umeda concerns intrasplenic immunization methods to generate anti-phospholipid antibodies, but only for use in investigating molecular mechanisms of PS interactions (Umeda at page 2273, column 2, second paragraph). The Office agrees that "Umeda does not teach the use of his antibodies in kits for diagnostic or therapeutic purposes" (fourth Action at page 10). Byers is also silent as to antibodies that bind to aminophospholipids.

Aside from describing methods to potentiate the cytotoxicity of immunotoxins, Byers is generally representative of the field of immunotoxins that bind to cancer cells, known in the art prior to the present invention. Indeed, the background section of the present application states

that immunotoxins for targeting cancer cells are known, but suffer from significant drawbacks. These include survival of antigen-negative or antigen-deficient cells that can repopulate the tumor or lead to further metastases, and the fact that a solid tumor is generally impermeable to molecules of the size of antibodies and immunotoxins, such that the physical diffusion distances and the interstitial pressure within the tumor are significant limitations to therapy with immunotoxins against cancer cells (see specification, *e.g.*, Description of the Related Art, fourth paragraph).

Agents that treat solid tumors by targeting the tumor vasculature, as in the present invention, represent a significant and surprising advance over immunotoxins that bind to tumor cells, as represented by Byers. Byers does not teach or suggest any aspect of tumor vasculature targeting, but simply represents part of the state of the art prior to the invention. The present invention further overcomes the problems associated with immunotoxins in themselves, as evident in Byers, with the surprising discoveries that naked antibodies against aminophospholipids specifically localize to the vasculature of solid tumors, induce tumor blood vessel destruction and cause tumor necrosis and destruction in the absence of conjugation to effector molecules, such as toxins or coagulants (see specification, *e.g.*, Summary of the Invention, first and second paragraphs).

As to combination treatments, Umeda does not teach the use of a first therapeutic agent (fourth Action at page 10), let alone a first and second. Gimbrone is alleged to disclose the use of a therapeutic conjugate alone "or in combination with other antibody or antibody fragment and/or a therapeutic agent (a second anti-cancer agent)" at column 15, lines 46-55 (fourth Action at page 9). In fact, Gimbrone at column 15, lines 46-55 concerns treating acute or chronic allograft rejection by administering an anti-E-selectin antibody, fragment or conjugate **alone**.

Thus, Gimbrone lacks any teaching or suggestion of a kit with first and second therapeutic agents of any type, and particularly fails to teach or suggest a kit with first and second anti-cancer agents.

The first, second and third references thus all fail to teach or suggest kits with two distinct anti-cancer agents, as required by the present claims. Indeed, the earlier § 103 rejection over Schroit, Gimbrone and Umeda has been withdrawn, the fourth Action attempting to rely on Byers to supply the required suggestion. However, Byers has been improperly combined with Schroit, Gimbrone and Umeda, and even if properly combined, still fails to teach or suggest the claimed invention.

Importantly, Byers is limited to methods to potentiate the cytotoxicity of immunotoxins (by triggering or enhancing endocytosis of the toxic moiety). This is an important difference from the presently claimed invention, in which the primary therapeutic agent is a naked, *i.e.*, unconjugated antibody, which does not suffer from any side effects associated with toxic moieties. Applicants appreciate that the unconjugated antibodies of the claimed kits can be combined with distinct immunotoxins, but this does not negate the lack of proper suggestion or in any way compensate for the irrelevance of Byers to the claimed invention.

For an obviousness rejection to be proper under 35 U.S.C. § 103, it is required that the cited prior art suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and that the prior art also convey to those of ordinary skill a reasonable expectation of success. *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

One of ordinary skill in the art would not consider Schroit, Gimbrone, Umeda and Byers, even if properly combined, as suggesting the presently claimed kits. Regarding Byers in particular, the ordinary skilled artisan would rather understand that Byers was limited to methods of potentiating the cytotoxicity of immunotoxins, and see no motivation in Byers to combine naked antibodies with other immunoglobulins, described only for use in enhancing endocytosis of the toxic moiety of the immunotoxin (Byers at column 6, lines 30-42). Only by using the present claims as a frame and the prior-art references as a mosaic could one piece together a facsimile of the claimed invention from Schroit, Gimbrone, Umeda and Byers. This is impermissible under the law. *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 USPQ 2d 1434, 1438 (Fed. Cir. 1988).

As Gimbrone and Umeda do not teach or suggest first and second anti-cancer agents, and as Byers is limited to methods of potentiating the cytotoxicity of immunotoxins, Gimbrone, Umeda and Byers are incapable of curing the admitted deficiencies of Schroit. For at least the foregoing reasons, claims 1, 3-12, 14, 19-29, 34, 35 and 39-48 are novel and non-obvious over Schroit, Gimbrone, Umeda and Byers, even if properly combined. Certain of the pending claims are also patentable over the cited references for various additional reasons.

Claims 39-42 recite kits in which the anti-aminophospholipid antibodies or fragments are functionally defined as binding to an aminophospholipid on the luminal surface of tumor vascular endothelial cells and as exerting particular anti-vascular effects. These claims are further patentable as the cited references do not teach or suggest the expression of aminophospholipids on the luminal surface of tumor blood vessels or anti-vascular effects of anti-aminophospholipid antibodies, let alone teach or suggest a kit comprising such antibodies in

combination with a second anti-cancer agent. Applicants pointed this out earlier, but the Office has yet to respond.

The surprising discovery that aminophospholipids are accessible, stable markers of tumor vasculature (specification at page 4, lines 29-30), as recited in claims 39-42, also underlies many surprising features of claims 1, 19-29, 34, 35 and 44-48. This finding in itself was particularly surprising, as the tumor vascular endothelial cells are normal cells, taught in the prior art to preserve PS in the inner leaflet (see Schroit at column 16, lines 28-31). Relatively stable PS expression at the cell surface of normal cells was not known prior to the present invention. Indeed, Schroit teaches away from the present invention by teaching that PS expression does not occur in normal cells. Despite the focus on diagnostics, Umeda also teaches away from the invention by teaching that PS resides only in the inner leaflet of normal cells (Umeda at column 5, lines 62-63).

The finding that PS was a marker of the normal cells of the tumor vasculature provided a means for effective therapy, overcoming the problems associated with tumor cell targeting, such as tumor cell resistance, antigen escape and effective penetration into the tumor. The inventors also unexpectedly discovered that naked antibodies against aminophospholipids are capable of specifically localizing to tumor vasculature and inducing tumor blood vessel destruction and tumor necrosis *in vivo* in the absence of conjugation to effector molecules. The invention thus provides single component therapeutics directed against tumor vasculature for use in the safe and effective treatment of solid tumors (specification at page 5, lines 5-10).

Importantly, the translocation of aminophospholipids to the surface of tumor vascular endothelial cells was further discovered to occur, at least in a significant part, independently of cell damage and apoptopic or other cell-death mechanisms (specification at page 5, lines 12-14).

This discovery of sufficiently stable expression on morphologically intact tumor-associated vascular endothelial cells, which is again in contrast to the prior art (as evidenced by Schroit), was an important step in the development of effective therapies (specification at page 5, lines 15-18).

In addition to providing effective anti-vascular tumor therapy with naked antibodies, as opposed to the difficulties associated with tumor cell targeting, the present discovery of sufficiently stable aminophospholipid expression on normal tumor vasculature endothelial cells gave rise to the combined anti-cancer therapeutics described in the present application and recited in the pending claims. In particular, a first antibody or fragment that binds to an aminophospholipid on the luminal surface of the vascular endothelial cells of the blood vessels of a vascularized tumor and another agent selected for "simultaneously or sequentially administering to the animal a therapeutically effective amount of at least a second anti-cancer agent" (specification from page 32, line 11 to page 33, line 12; see also **Section J** of the specification). Therefore, the present invention, unlike the cited prior art, provides for the intelligent selection of first and second anti-cancer agents in a kit for use together.

These aspects of the invention are highlighted in claims 44-48, which are directed to therapeutic kits in which the second anti-cancer agent is selected for combined use according to the guidance provided in the specification. A second anti-cancer agent administered at a biologically effective time *prior* to the anti-aminophospholipid antibody is taught to (i) increase aminophospholipid expression, or injure or induce apoptosis in the tumor blood vessel endothelium (specification at page 33, lines 5-12); whereas a second anti-cancer agent administered at a biologically effective time *subsequent* to the anti-aminophospholipid antibody is

taught to (ii) kill tumor cells or to be an anti-angiogenic agent that inhibits metastasis of tumor cells (specification from page 32, line 27 to page 33, line 3).

Schroit, Gimbrone, Umeda and Byers, even if properly combined, do not teach or suggest anti-cancer agents that increase aminophospholipid expression, injure or induce apoptosis in tumor blood vessel endothelium, or that kill or inhibit the metastasis of tumor cells, let alone teach or suggest such agents as the second anti-cancer agent in a kit comprising a first anti-cancer agent in the form of an unconjugated antibody or fragment thereof that binds to an aminophospholipid on the luminal surface of the vascular endothelial cells of the blood vessels of a vascularized tumor. The present application, in contrast, teaches the rationale for selecting such agents in combination along with detailed teaching concerning second anti-cancer agents within each category.

Applicants' last two responses have provided actual data to support the reasoning in the application, showing that various factors and tumor-associated conditions known to be present in the tumor microenvironment are able to cause PS translocation in cultured endothelial cells. Hypoxia/reoxygenation, acidity, thrombin, and inflammatory cytokines, such as IL-1α, IL-1β, TNFα and IFN, are all shown to induce PS exposure without causing cytotoxicity. Hydrogen peroxide is also shown to be a strong inducer of PS, and inflammatory cytokines and hypoxia-reoxygenation are shown to have greater than additive effects, supporting the inventors' surprising findings that factors in tumors interact to give amplified effects on PS-exposure on the normal tumor vascular endothelial cells *in vivo*.

The foregoing information, and its effective use to provide the kits of the claimed invention, exists in the present application but not in the cited art. Applicants have emphasized this in their last two responses to § 103(a) rejections, both in regard to claims 1, 19-29, 34, 35

and 44-48 and claims 39-42. The Office has neither responded to any of this reasoning, nor explained why the rejection is globally applied to all claims without reference to the various unique features recited in different claims. This is improper.

Claim 49, drawn to kits in which the first anti-cancer agent is an antibody or fragment that binds to phosphatidylethanolamine, is further patentable, as the cited references do not teach or suggest a therapeutic antibody that binds to phosphatidylethanolamine, let alone such an antibody as part of a kit in combination with a second, distinct anti-cancer agent. Moreover, Schroit teaches away from these aspects of the invention by the stated objective to produce highly-specific anti-PS antibodies (Schroit at column 2, line 36) and by the description of the resultant antibodies as being able to recognize PS but not DPOE (dioleoyl phosphatidylethanolamine) in a bilayer membrane (Schroit at column 25, lines 24-26).

The rejection of all claims under 35 U.S.C. § 103(a) is thus overcome and should be withdrawn.

IX. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance and such favorable action is respectfully requested. Should Examiner Sharareh have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,
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